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B. Webb
1/24/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Susan L. Weston et al. Art Unit: 1655

Serial No.: 09/228,639 Examiner: Enewold, J.

Date Filed: January 12, 1999 Docket No.: 13131

For: Sequences

Dated: January 22, 2002

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Assistant Commissioner for Patents
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PRELIMINARY AMENDMENT

Sir:

This preliminary amendment is filed in connection with the above-identified patent application in response to the final Office Action mailed October 13, 2000.

REMARKS

Pending Claims

Claims 1, 2, 3, 5 and 12-18 are pending in the application. Applicants thank the Examiner for withdrawing the previous claim rejections under 35 U.S.C. 112, second paragraph, and for considering all the claims on their merits.

Rejection Under 35 U.S.C. 103(a):

The Examiner maintains the previous rejection of claims 1-3, 5, and 10-16 under 35 U.S.C. 103(a) as being unpatentable over Little et al. and Ferrie et al. in

view of Estivill et al. and CFGAC (see June 14, 2000 Office Action). The Examiner had contended in the previous rejection that Little discloses that the ARMS method can be used to selectively amplify multiple sites and may be useful for screening a single sample for multiple nucleotide variations, and that primers for the cystic fibrosis gene can be used. Ferrie discloses the development of an ARMS test for common mutations of the CTFR gene. The Examiner admitted in the previous rejection that neither Little nor Ferrie disclose the specific combination of primers taught by the present invention. However, the Examiner cited the Estivill and CGFAC references as disclosing the mutations used to generate the instant invention's primers. The Examiner maintains the previous contention that it would have been *prima facie* obvious, in the absence of secondary considerations, to one of ordinary skill in the art to have modified the disclosures of Little and Ferrie in view of Estivill and CGFAC to arrive at the present invention.

Applicants respectfully disagree. There is no teaching or suggestion in the cited prior art that would allow one of ordinary skill in the art to combine the cited references to obtain the diagnostic method of the invention using new primer sets specifically for the twelve known CTFR mutations of the invention, or to obtain the specific primer sets themselves. Applicants are not claiming individual primers. Instead, Applicants claim sets of primers as well as a method of using sets of primers for detecting a total of twelve CFTR mutations. Although Little discloses ARMS multiplexing of certain cystic fibrosis gene mutations using some of the same primers disclosed in the present invention, and Ferrie discloses multiplex ARMS testing methods for common CFTR gene mutations, there is no teaching or suggestion in Little or Ferrie, taken alone or in combination, to use the primers in the specific groupings, or sets, disclosed in the present invention. Furthermore, although Estivill and CFGAC disclose the CFTR mutations corresponding to the claimed primers and their relative frequencies in various populations, the Examiner has not provided any evidence that one of ordinary skill in the art would be motivated to combine Estivill and CFGAC with Ferrie and Little to screen for the particular primer sets of the present invention.

Instead of providing any such evidence of any disclosure or suggestion to combine the cited references, the Examiner argues that the ordinary artisan would have been able to perform routine experimentation to optimize the ARMS systems desired for the particular situation, based upon the cited references. Since the sequences of the CFTR gene mutations were known (Estivill and CFGAC) at the time the present invention was made, the Examiner contends that generating primers for these regions would have been obvious over Little and Ferrie, which disclose the properties of the primers needed for the ARMS assay. The Examiner cited *In re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995) stating that "a prima facie case of obviousness in based upon structural similarity....a prior art compound may suggest its homologs ...and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." The Examiner then states that the claimed primers are structural homologs of the full length disclosed CFTR nucleic acid sequence, and that a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties. For these reasons, the Examiner contends that the claimed primers are prima facie obvious over the cited references in the absence of secondary considerations.

Applicants respectfully disagree with the Examiner. Primers are not homologs of genes. Instead, a primer is an extendable chain of nucleic acid, where an additional nucleic acid can be added to the chain using a polymerase. Homologs are not used in the biological arts to compare different classes of nucleic acids such as primers and genes.

In the present case, the compounds previously disclosed, such as the CFTR mutations and certain primers to these mutations, do not suggest the design of appropriate diagnostic primers or sets of primers. Knowledge of a template sequence does not render the design of such primers obvious. *In re Deuel* states "in all of these prima facie cases, the prior art teaches a specific structurally-definable compound and the question becomes ***whether the prior art would have suggested making the specific molecular modifications*** necessary to achieve the claimed invention." *Id.*

There is simply no disclosure or suggestion in any of the references, alone or in combination, of the specific primers of the present invention, i.e., having the lengths, concentrations and combinations taught by the present invention and methods

of using of these primers in multiplex analysis with the unexpectedly optimal results demonstrated in the specification (see Examples 1, 2 and Table 2).

The rejection as obvious over the prior art cannot be founded on an impermissible "obvious to try" standard, i.e. to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gives only general guidance as to how to achieve the claimed invention. For an invention to be obvious over the prior art, the prior art must teach or suggest the invention. The Examiner is using an impermissible hindsight reconstruction of the claimed invention based upon a general motivation to search for primers.

In the present case, the particular sets of primers disclosed in the present invention are unique and non-obvious. As the Examiner acknowledges, neither Little nor Ferrie disclose the specific combination of primers taught by the present invention. Ferrie and Little may provide general guidance as to how to design multiplex ARMS tests, but there is no motivation to combine Little or Ferrie's disclosures with those of the Estivill and CGFAC references, which teach CFTR mutations in general populations, to obtain the particular sets of primers claimed in the present invention.

Instead of disclosing the present invention, Ferrie teaches away from a test that uses more than the four primers. Ferrie states that there are practical limits to the number of samples that can be routinely analyzed for CF mutations (page 252). In response to this argument, the Examiner asserts that Ferrie does not teach practical limits of the ARMS test, but instead is teaching that studying all 150 mutations in a multiplex is out of the practical limits (page 252, col. 1). This is a misinterpretation of Ferrie's statement on page 252, column 1, where he states "[S]ince the discovery that ΔF508 was the major CF mutation, over 150 further CF mutations have been reported to the Cystic Fibrosis Genetic Analysis Consortium. Although it is often desirable to analyze samples for as many CF mutations as possible, there are practical limits to the number which can routinely be performed."

Moreover, Ferrie does not state anywhere that studying all 150 mutations in a multiplex is out of the practical limits, but instead that there are practical limits to the

number which can be performed. Read in the context of the entire article, which further addresses the difficulty of multiplexing primers directed to just four mutations (p.260), it is clear that Ferrie, suggests that studying more than approximately four mutations in a multiplex would be outside the practical limits. The present invention teaches multiplex reactions comprising more than four sets of primers, i.e. six sets in each of two vessels, and teaches the unexpectedly successful multiplexing of up to twelve primers.

The Examiner further argues that Schumm et al. (US Pat. No. 5,843,660) discloses the multiplexing of eight short tandem repeat (STR) loci and that successful combinations can be generated by trial and error of locus combinations, by selection of primer pair sequences, and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified. The Examiner concludes that the art (Schumm) has disclosed the multiplexing of eight different loci in a single reaction vessel and thus, six primer sets of the instant invention is well within the realm of practical limits. (Office Action, p. 8)

With regards to Schumm, a person of ordinary skill in the art would not be motivated to combine this reference with the others cited because its focus is STR (short tandem repeat) loci, which is different than the focus of the present invention on the CFTR genetic mutations. STR loci are regions of the human genome that contain short, repetitive sequence elements of 3 to 7 base pairs in length. Schumm discloses that polymorphic STR loci are extremely useful markers for human identification, paternity testing and genetic mapping. Schumm discloses that while there are multiplex amplification procedures for specific loci, the use of multiplex amplification procedures is greatly desired for the detection of alleles in other types of loci such as specific STR loci and that it is also desirable to identify primers which make multiplex amplification of such loci possible (col. 3, lines 45-50). Schumm merely cites Ferrie as a general reference discussing multiplex amplification sets for analysis of genes related to human genetic diseases. The STR analysis described by Schumm yields a measure of genetic diversity, but it does so without determining the identity of any disease causing mutation. Since Schumm distinguishes STR loci from

those related to human genetic disease, one of ordinary skill in the art would not be motivated to combine Schumm with Ferrie or any of the other cited references.

In the previous response, Applicants noted that Ferrie, at page 260, disclosed the difficulty of multiplexing primers directed to just four mutations. Ferrie further disclosed on page 260 the difficulties associated with multiplexing primers. The Examiner responds that statements regarding unpredictability of the art at the time the invention was made must be supported by evidence, not argument, provided in an appropriate affidavit or declaration. However, Applicants note that such evidence is in a reference relied upon by the Examiner. Further, the references themselves express the long-felt need for the present invention.

The Examiner maintains that although Ferrie discloses potential difficulties with multiplexing primers, Ferrie also suggests to the ordinary artisan how to overcome these difficulties through routine experimentation (i.e., altering primer sequence, concentration and longer primers lead to optimal results).

Applicants maintain that the claimed sets of primers unexpectedly work together in the multiplex ARMS reaction to detect the presence or absence of twelve known CFTR mutations. These sets of primers are able, unexpectedly, to detect the specific mutations reliably and robustly, as shown in the specification, particularly in Table 2 and in Examples 1 and 2

Further, Applicants note that the primers and conditions disclosed were the surprising or unexpected results of research by the inventors, monthly reports are attached to the accompanying Declaration. Since the Examiner also noted that the MPEP makes clear that statements regarding unexpected results must be supported by an appropriate affidavit or declaration, Applicants submit a Declaration under 37 C.F.R. 1.132, executed by (Dr. Gary Brown from Orchid BioSciences, Inc. the new assignee of the present invention) one skilled in the art and knowledgeable about the invention disclosed.

In view of the above amendments, the above discussion of the claims, and the Declaration under 37 C.F.R. 1.132, Applicants maintain that the cited references, alone or in combination, do not disclose, teach or suggest the present invention. Accordingly, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103, be reconsidered and withdrawn.

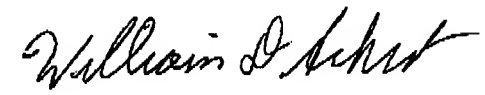
CONCLUSION

All of the stated grounds of the rejections have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that the present application is in condition for Allowance.

If a telephone conference would be of assistance in furthering the prosecution of the application, Applicants' undersigned attorney requests that he be contacted at the telephone number provided below.

If additional fees are deemed necessary for the filing of this Amendment, authorization is hereby given to charge any such fees to Deposit Account No. 11-0171. Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,



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